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Efficacy and Safety of Pharmacokinetically Enhanced Amoxicillin-Clavulanate at 2,000/125 Milligrams Twice Daily for 5 Days versus Amoxicillin-Clavulanate at 875/125 Milligrams Twice Daily for 7 Days in the Treatment of Acute Exacerbations of Chronic Bronchitis

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This randomized, controlled trial was designed to show that a short, 5-day course of pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 mg (Augmentin XR) is as effective clinically as a longer, 7-day course of conventional amoxicillin-clavulanate at 875/125 mg (both given twice daily) in the treatment of acute exacerbations of chronic bronchitis (AECB). Amoxicillin-clavulanate at 2,000/125 mg was designed to extend the therapeutic levels of amoxicillin in serum over the 12-h dosing interval, compared with conventional formulations, to eradicate bacterial strains for which amoxicillin MICs were ≤4 μg/ml while retaining efficacy against β-lactamase-producing pathogens. A total of 893 patients were randomized and received study medication (amoxicillin-clavulanate at 2,000/125 mg for 443 patients and 875/125 mg for 450 patients). Overall, 141 patients receiving amoxicillin-clavulanate at 2,000/125 mg and 135 receiving the comparator formulation had at least one pathogen identified at screening. Amoxicillin-clavulanate at 2,000/125 mg was as effective clinically in the per-protocol (PP) population at the test of cure (days 14 to 21, primary efficacy endpoint) as amoxicillin-clavulanate at 875/125 mg (clinical success rates of 93.0 and 91.2%, respectively; treatment difference, 1.8; 95% confidence interval [CI], −2.2, 5.7). Bacteriological success in the bacteriology PP population was high for both formulations (amoxicillin-clavulanate at 2,000/125 mg, 76.7%; amoxicillin-clavulanate at 875/125 mg, 73.0%; treatment difference, 3.8; 95% CI, −7.5, 15.0). Both therapies were well tolerated, with a similar incidence of adverse events. Fewer than 5% of patients in each group withdrew from the study due to adverse events. The shorter, 5-day course of amoxicillin-clavulanate at 2,000/125 mg was shown to be as effective clinically as a longer, 7-day course of amoxicillin-clavulanate at 875/125 mg, with high bacteriological efficacy and no difference in tolerability.

Chronic bronchitis and acute exacerbations of chronic bronchitis (AECB) are common respiratory complaints, accounting for up to 14 million physician visits annually in the United States (17). In the United States, the annual treatment cost of AECB has been estimated at greater than $1.5 billion (26). AECB-related feelings of panic and dread, dependence on medication, reduced self-esteem, and embarrassment about symptoms were identified as factors reducing patients' perceived quality of life (25).

The role of bacterial pathogens in AECB is controversial. However, it has been estimated that as many as 50 to 70% of AECB episodes are bacterial in origin (5). The primary pathogens thought to be involved in AECB are *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus parainfluenzae* (6, 7, 12). An increasing prevalence of resistance to commonly prescribed antimicrobials has been documented among isolates of *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*. In the period 1998 to 2000, β-lactamase production was reported in 16.9% of *H. influenzae* and ≥90% of *M. catarrhalis* isolates worldwide (19). The prevalence of penicillin-resistant *S. pneumoniae* (PRSP; penicillin MICs of ≥2 μg/ml) has greatly increased in recent years, with as many as 15% of *S. pneumoniae* isolates from patients with AECB in one surveillance study (1999 to 2000) being resistant to penicillin (28).

Pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 mg (available in the United States as Augmentin XR) was designed by using pharmacokinetic/pharmacodynamic principles to eradicate strains of PRSP for which amoxicillin MICs are at least 4 μg/ml (20). For β-lactam antimicrobials, the time above MIC ($T >$ MIC) of the infecting pathogen is the key indicator for predicting bacteriological efficacy, and for amoxicillin and amoxicillin-clavulanate, a $T >$ MIC of 35 to 40% of the dosing interval is predictive of maximum bacteriological efficacy (8, 9, 10, 23, 32). The sustained-release technology of amoxicillin-clavulanate at 2,000/125 mg provides therapeutic levels of amoxicillin in serum for a greater proportion of the dosing interval ($T >$ MIC of 49.4% for a MIC of 4 μg/ml) than is achieved with immediate-release formulations, thus increasing the amoxicillin $T >$ MIC without affecting the pharmacokinetic properties of clavulanate (20). Pharmacokinetically enhanced amoxicillin-clavulanate is administered as two bilayer tablets every 12 h. Each tablet contains one layer of immediate-release amoxicillin trihydrate equivalent to 562.5

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mg of amoxicillin plus potassium clavulanate equivalent to 62.5 mg of clavulanic acid, as well as one layer of sustained-release crystalline sodium amoxicillin equivalent to 437.5 mg of amoxicillin (20).

Standard amoxicillin-clavulanate therapy usually consists of 7 days of medication. As studies of other commonly used therapies have demonstrated comparable efficacy of short-course therapy to standard therapy in AECB (1, 16, 22, 29), the present study was undertaken to investigate the efficacy of a short-course, 5-day treatment regimen of the new, pharmacokinetically enhanced formulation of amoxicillin-clavulanate compared with a standard, 7-day treatment regimen of amoxicillin-clavulanate at 875/125 mg in patients with AECB. The efficacy of amoxicillin-clavulanate demonstrated in previous AECB studies indicates that both therapies should be effective in treating patients in the current study and that the 5-day therapy with amoxicillin-clavulanate at 2,000/125 mg would be at least as effective as 7 days of therapy with amoxicillin-clavulanate at 875/125 mg.

MATERIALS AND METHODS

Study design. This randomized, double-blind, double-dummy, parallel group study was carried out in 85 centers in Belgium, Canada, Czech Republic, France, Germany, Hong Kong, Pakistan, Philippines, Poland, Romania, Singapore, Switzerland, Taiwan, and the United States from November 2001 to May 2002. The study was conducted in accordance with *Good Clinical Practice and the Declaration of Helsinki* as amended in Somerset West, Republic of South Africa, in 1996. The protocol was approved by national, regional, or center ethics committees or institutional review boards, as appropriate, for each participating center. All patients gave written, dated informed consent prior to study entry.

Patient selection and randomization. Male and female patients with AECB, as defined by Anthonisen et al. (3), characterized by increased purulent sputum with increased cough and increased dyspnea were eligible for inclusion in the study if they were either $\geq$45 or $\geq$40 years of age and had 15 or more smoking pack years and had a history of chronic bronchitis characterized by cough and sputum production for $\geq$2 consecutive years and for most days in a consecutive 3-month period in each year. Patients were required to provide a sputum sample or, where clinically indicated, an invasive respiratory sample and be willing and able to comply with the study protocol. Female patients of childbearing potential or $<$1 year postmenopausal had to have a negative urine pregnancy test prior to enrollment and be using an acceptable method of birth control during the study period.

Reasons for exclusion related to underlying disease included clinical and radiological diagnosis of pneumonia, cystic fibrosis, active tuberculosis, radiological and clinical signs of bronchiectasis, active pulmonary malignancy, infectious mononucleosis, known and/or suspected renal or hepatic impairment (due to the potential for drug-related toxicity in patients with such a condition), including the presence of hepatitis B surface antigen, a complicating disease or infection that would compromise evaluation of the study medication, or an unstable life-threatening or serious underlying disease. Patients who were immunocompromised or known to be human immunodeficiency virus positive with a CD_4 count of $<$200 cells/mm^3 were also excluded.

The use of certain concomitant medications was prohibited, including current or scheduled receipt of systemic corticosteroids at a dose of $>$10 mg/day of prednisone or equivalent, the commencement of mucolytic therapy, concomitant renal tubular secretion inhibitors, allopurinol, or abuse of drugs or alcohol. Patients were not included in the study if they had received an investigational drug or vaccine within 30 days or 5 half-lives prior to study entry or if they had been treated with any other systemic antibacterial within 7 days prior to study entry.

Patients were excluded from the study if they had a known or suspected hypersensitivity to penicillin or other β-lactam antibacterials, a history of amoxicillin-clavulanate-associated cholestatic jaundice or hepatic dysfunction, or had been previously enrolled in this or any other study involving pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 mg. Female patients who were pregnant, lactating, planning a pregnancy during the study period, or using inadequate methods of birth control were also excluded.

Patients who fulfilled the study entry criteria were randomized (1:1) to receive either oral amoxicillin-clavulanate at 2,000/125 mg (given as two 1,000/62.5-mg tablets) twice daily for 5 days and an oral amoxicillin-clavulanate 875/125-mg placebo twice daily for 7 days or oral amoxicillin-clavulanate at 875/125 mg twice daily for 7 days and a 2,000/125-mg placebo (given as two tablets) twice daily for 5 days.

Patient assessment. Patients were required to attend the clinic five times for assessment at screening (day 0), on therapy (day 3 to 5), at the end of therapy (days 9 to 11), at test of cure (days 14 to 21), and at long-term follow-up (days 28 to 35). Patients who withdrew from the study prematurely were asked to return for a safety follow-up visit (days 28 to 35).

Historic forced expiry volume over 1 s (FEV_1) and forced vital capacity (FVC) measurements taken within the 12 months prior to study entry were recorded at the screening visit. If no historic lung function test results were available, FEV_1 and FVC were measured at the long-term follow-up visit (or within the 5 days prior to that visit) for patients no longer suffering an exacerbation. Lung function test results and recorded symptoms were assessed according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria (27) and were used to categorize a patient's severity of disease.

A clinical outcome of "success" at the end-of-therapy, test-of-cure, and long-term follow-up visits was defined as the sufficient improvement or resolution of the signs and symptoms of AECB recorded at the screening such that no additional antibacterial therapy was prescribed for the episode of AECB. A clinical outcome of "failure" at the end-of-therapy visit was defined as insufficient improvement or deterioration of signs and symptoms of AECB such that additional antibacterial therapy was prescribed for AECB. These endpoints accounted for the fact that patients for whom investigators determined study therapy was ineffective most likely would be given additional therapy to resolve the current episode of AECB. Additionally, the nature of the underlying lung disease could affect the rate of lung function improvement, making lung function tests an inadequate measure of treatment efficacy, as improved lung function may not have occurred immediately following resolution of the acute infection. At the test-of-cure and long-term follow-up visits, an outcome of "clinical recurrence" was defined as the reappearance or worsening of signs and symptoms of AECB for patients who were clinical successes at the previous visit, such that additional antibacterial therapy was prescribed for AECB. An outcome of "unable to determine" was made if an assessment of clinical outcome could not be made (e.g., the patient was lost to follow-up or did not consent to clinical examination). Patients with a clinical outcome of "unable to determine" were assigned a clinical response of failure. A patient recorded as a clinical failure at any visit was automatically recorded as a clinical failure at all subsequent visits.

A bacteriological response of success was recorded at end of therapy if the screening pathogen was eradicated (absence of the screening pathogen in an evaluable sputum or respiratory sample) or if there was clinical evidence of eradication in the absence of an evaluable sputum or respiratory sample and there was no new infection. At the test-of-cure and long-term follow-up visits, a response of success was recorded if the above criteria were met and the patient was considered a bacteriological success at all previous visits.

A bacteriological response of failure was recorded at the end-of-therapy visit if the pathogen isolated at screening was still present in an evaluable sputum or respiratory sample or, if the patient did not have an evaluable sample, the patient had a clinical outcome of "failure" at the end-of-therapy visit. Patients who had a new pathogen isolated in a sputum or respiratory sample at the end of therapy and were symptomatic for AECB were given a bacteriological response of "failure." Patients who had a clinical outcome of "unable to determine" and who did not have an evaluable sputum or respiratory sample received a bacteriological outcome of "unable to determine." These were automatically recorded as a bacteriological failure in the intent-to-treat (ITT) population. At the test-of-cure and long-term follow-up visits, patients were recorded as bacteriological failures if they had a bacteriological response of failure at any previous visit or if they had a response of success at an earlier visit but had a recurrence of the initial pathogen or infection with a new pathogen and were symptomatic or had an outcome of "unable to determine" at the subsequent visit.

Bacteriology. Sputum samples or, if clinically indicated, invasive respiratory samples were obtained at screening prior to the first dose of study medication and, where possible, at the end of therapy. If the patient was a clinical success at the previous visit, a sample was also obtained, if possible, at the test-of-cure and long-term follow-up visits. If the patient was withdrawn at the on-therapy visit, a sample was obtained at that visit.

Sputum samples were evaluated by Gram stain for purulence, defined as $<$10 squamous epithelial cells and $>$25 leukocytes per $\times$100 microscopic field. A sputum sample had to be purulent to be considered evaluable for routine culture. All samples collected by invasive means were considered evaluable. Evaluation of samples did not distinguish between infection and possible colonization for the

TABLE 1. Patient demographic characteristics at screening of the ITT and clinical PP populations

Demographic characteristic	Amoxicillin-clavulanate treatment group			
	ITT population		Clinical PP population	
	2,000/125 mg (n = 443)	875/125 mg (n = 450)	2,000/125 mg (n = 357)	875/125 mg (n = 353)
Gender (male); n (%)	289 (65.2)	289 (64.2)	227 (63.6)	225 (63.7)
Age (yr)				
Mean (SD)	60.1 (11.3)	60.3 (11.5)	60.1 (11.2)	60.1 (11.5)
Range	33–88	32–90	36–88	38–90
Race; n (%)				
White	380 (85.8)	382 (84.9)	309 (86.6)	301 (85.3)
Black	29 (6.5)	30 (6.7)	24 (6.7)	27 (7.6)
Oriental	24 (5.4)	27 (6.0)	18 (5.0)	17 (4.8)
Other[a]	10 (2.3)	11 (2.4)	6 (1.7)	8 (2.3)
Smoking history; n (%)				
Current smoker	189 (42.7)	181 (40.2)	156 (43.7)	148 (41.9)
Have ever smoked	340 (76.7)	345 (76.7)	274 (76.8)	278 (78.8)
Smoking pack yr; n (%)				
0	103 (23.3)	105 (23.3)	83 (23.2)	75 (21.2)
>0–10	39 (8.8)	42 (9.3)	32 (9.0)	33 (9.3)
>10–20	63 (14.2)	54 (12.0)	47 (13.2)	43 (12.2)
>20–30	69 (15.6)	78 (17.3)	55 (15.4)	62 (17.6)
>30	165 (37.2)	168 (37.3)	138 (38.7)	139 (39.4)
Unknown	4 (0.9)	3 (0.7)	2 (0.6)	1 (0.3)

[a] Hispanic, Indian, Asian, American Indian, and unknown.

pathogens isolated, with the exception of coagulase-negative *Staphylococcus*, viridans group streptococci, *Corynebacterium* spp., nonpathogenic *Neisseria* spp., *Stomatococcus* spp., *Micrococcus* spp., and nonhemolytic *Streptococcus* spp., as these are all considered normal flora.

Evaluable samples were cultured by a local laboratory for the presence of aerobic bacteria and identification of isolates to the genus and species level. All respiratory pathogens isolated by the local laboratory were sent to the central laboratory for confirmation of identification by routine procedures. MICs for aerobic organisms were determined by a broth dilution method according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines (24) and the recommendations of the manufacturer (Trek Diagnostic Systems, West Sussex, United Kingdom). Disk diffusion testing was also conducted with amoxicillin-clavulanic acid on aerobic pathogens following NCCLS guidelines (24). Susceptibility was then determined with NCCLS breakpoints (24). Amoxicillin-clavulanic acid was tested in a 2:1 ratio; the MICs reported are based on the amoxicillin content. The NCCLS breakpoints for conventional amoxicillin-clavulanic acid formulations were used to interpret results as there are no NCCLS breakpoints for the 2,000/125-mg formulation at this time. Testing of *Haemophilus* spp., *M. catarrhalis*, *Enterococcus* spp., and *S. aureus* for the presence of β-lactamase was carried out with the nitrocefin disk methodology (Becton Dickinson, San Jose, Calif.), and *S. aureus* was tested for methicillin resistance by oxacillin (1 μg) disk diffusion (Becton Dickinson, Sparks, Md.).

Quality controls for both susceptibility testing methods were performed with American Type Culture Collection strains according to NCCLS guidelines (24).

Safety assessment. The screening visit included measurement of vital signs (temperature, pulse rate, and respiration rate), a blood sample for hematology and clinical chemistry evaluation, and urinalysis. Vital signs were also recorded at each subsequent visit. Adverse events (AEs) and serious adverse events (SAEs) were recorded on therapy and for 30 days after therapy for all patients who received ≥1 dose of study medication (ITT population) and were assessed for frequency, duration, severity, outcome, and relationship to study medication.

AEs were not limited to incidents or conditions relating to study medication and may have included exacerbations of preexisting conditions, concurrent illnesses, drug interactions, or the significant worsening of the disease under investigation. SAEs were any AEs considered to be life threatening, disabling, or incapacitating; associated with congenital abnormality, cancer, or overdose (accidental or intentional); or that resulted in or prolonged a hospital stay or any event that the investigator regarded as serious or that would suggest a significant hazard associated with the use of study medication.

Statistical analysis. A total of four patient groups were identified for efficacy analysis. The ITT population comprised all randomized patients who took at least one dose of study medication. The clinical per-protocol (PP) population was a subset of the ITT population and excluded patients who violated any aspect of the study protocol to a degree or extent that might affect assessment of treatment efficacy. This was the primary population of interest. Possible protocol violations that might affect assessment were determined prior to the commencement of the study and included violation of exclusion criteria (including age), serious or complicating infection or disease, active alcohol or drug abuse, use of prohibited concomitant medication, compromising adverse event, medication or visit noncompliance, not having AECB, and an outcome of "unable to determine." Exclusions from analysis, where warranted, were applied after study completion and prior to unblinding. The bacteriology ITT population included all randomized patients who took at least one dose of study medication and had at least one pretherapy pathogen identified at screening. The bacteriology PP population was a subset of the bacteriology ITT population and excluded those patients who violated any aspect of the study protocol to an extent that might affect assessment of treatment efficacy.

The primary efficacy parameter was the clinical response at the test-of-cure visit. The secondary efficacy parameters were clinical response at the end-of-therapy and long-term follow-up visits and bacteriological response at test of cure, end of therapy, and long-term follow-up.

The study was designed to enroll 900 patients to provide 674 who would be evaluable (337 in each treatment arm), thus providing the number of patients required to give a power of 90% with the lower side of the 95% confidence interval no less than −10%. This assumed an underlying equivalent clinical response rate of 80% and that up to 25% of enrolled patients would be ineligible for the PP population.

The primary efficacy analysis was based on an unstratified comparison of proportions between the treatment groups in the clinical PP population. A two-sided 95% confidence interval (CI) was used to estimate the difference in the proportion of successes between the two groups. A conclusion of non-inferior efficacy of pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 mg twice daily for 5 days compared with amoxicillin-clavulanate at 875/125 mg twice daily for 7 days was reached if the lower limit of the CI (group with amoxicillin-

TABLE 2. Patient clinical characteristics at screening of the ITT and clinical PP populations

Clinical characteristic	Amoxicillin-clavulanate treatment group[a]			
	ITT population		Clinical PP population	
	2,000/125 mg (n = 443)	875/125 mg (n = 450)	2,000/125 mg (n = 357)	875/125 mg (n = 353)
Duration of chronic bronchitis (yr)				
Mean (SD)	10.7 (8.4)	11.2 (9.6)	10.7 (8.5)	11.0 (9.5)
Range	1.1–57.2	0.0–58.2	2.0–57.2	2.0–58.2
Baseline FEV_1 (% predicted); n (%)				
<50%	101 (22.8)	107 (23.8)	84 (23.5)	85 (24.1)
50–70%	101 (22.8)	104 (23.1)	86 (24.1)	91 (25.8)
>70%	173 (39.1)	163 (36.2)	143 (40.1)	130 (36.8)
Unknown	68 (15.3)	76 (16.9)	44 (12.3)	47 (13.3)
Baseline FEV_1/FVC; n (%)				
<50%	43 (9.7)	47 (10.4)	36 (10.1)	34 (9.6)
50–70%	109 (24.6)	106 (23.6)	92 (25.8)	92 (26.1)
>70%	223 (50.3)	221 (49.1)	185 (51.8)	180 (51.0)
Unknown	68 (15.3)	76 (16.9)	44 (12.3)	47 (13.3)
No. of exacerbations treated with antimicrobials in previous yr; n (%)				
0	70 (15.8)	70 (15.6)	56 (15.7)	54 (15.3)
1–4	325 (73.4)	326 (72.4)	262 (73.4)	257 (72.8)
>4	47 (10.6)	54 (12.0)	39 (10.9)	42 (11.9)
Unknown	1 (0.2)	0	0	0
Use of systemic corticosteroids in previous yr; n (%)				
Yes	71 (16.0)	96 (21.3)	56 (15.7)	73 (20.7)
No	372 (84.0)	354 (78.7)	301 (84.3)	280 (79.3)
Sputum characteristics; n (%)				
Increased volume of purulent sputum	443 (100)	449 (99.8)	357 (100)	353 (100)
Increased sputum purulence	404 (91.2)	412 (91.6)	326 (91.3)	328 (92.9)
Increased cough; n (%)	443 (100)	449 (99.8)	357 (100)	353 (100)
Increased dyspnea; n (%)	441 (99.5)	449 (99.8)	357 (100)	353 (100)
Duration of current exacerbation (days)				
Mean (SD)	8.8 (13.1)	8.6 (11.6)	8.8 (12.9)	7.8 (10.1)
Range	0–120	1–120	0–120	1–120
Hospital in-patient at time of study; n (%)	31 (7.0)	30 (6.7)	27 (7.6)	26 (7.4)

[a] Percentages may not add up to 100% due to rounding.

clavulanate at 2,000/125 mg − group with amoxicillin-clavulanate at 875/125 mg) was no less than −10%. The study was not powered to provide statistically significant results at secondary endpoints.

RESULTS

Patient disposition. A total of 900 patients were randomized, of whom 893 received at least one dose of study medication (amoxicillin-clavulanate at 2,000/125 mg, 443 patients; amoxicillin/clavulanate at 875/125 mg, 450 patients) and were included in the ITT and safety populations. The demographic profiles of the two groups were similar (Table 1). The mean patient age was approximately 60 years, and there were more males than females in both treatment groups. Baseline clinical characteristics were also similar between the two groups (Table 2). There were slightly more patients in the amoxicillin-clavulanate 875/125-mg group than in the amoxicillin-clavulanate 2,000/125-mg group that had used systemic corticosteroids in the previous year (21.3 and 16.0%, respectively). The majority of patients in both treatment groups had experienced between one and four exacerbations treated with antibacterials within the previous year before study entry. In general, there were no major differences between the ITT and PP populations. Of patients in the ITT population who had a GOLD score calculated (those with post-bronchodilator FEV_1 and FVC measurements), 8.0% (19 of 238) in the amoxicillin-clavulanate 2,000/125-mg treatment group and 5.8% (13 of 226) in the amoxicillin-clavulanate 875/125-mg treatment group had a classification of "severe," based on GOLD criteria and defined as "severe airflow limitation" (FEV_1 <30% predicted) or the presence of respiratory failure or clinical signs of right heart failure." A modified GOLD score was calculated for a further 749 patients in the ITT population and, of these, 6.9% (26 of

TABLE 3. Number of patients with key[a] pathogens isolated at screening of the bacteriology ITT and PP populations

Pathogen	No. (%) of patients in amoxicillin-clavulanate treatment group[b]			
	Bacteriology ITT population		Bacteriology PP population	
	2,000/125 mg (n = 141)	875/125 mg (n = 135)	2,000/125 mg (n = 116)	875/125 mg (n = 111)
H. parainfluenzae	41 (29.1)	42 (31.1)	34 (29.3)	37 (33.3)
H. influenzae	33 (23.4)	37 (27.4)	29 (25.0)	32 (28.8)
S. pneumoniae	28 (19.9)	22 (16.3)	22 (19.0)	18 (16.2)
Methicillin-susceptible *S. aureus*	17 (12.1)	12 (8.9)	14 (12.1)	10 (9.0)
M. catarrhalis	13 (9.2)	16 (11.9)	8 (6.9)	11 (9.9)

[a] Other pathogens identified in >1 patient: *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Klebsiella oxytoca*, β-hemolytic *Streptococcus* group B, *Enterobacter cloacae*, β-hemolytic *Streptococcus* group F, *Citrobacter freundii, Enterobacter aerogenes, Klebsiella ozaenae, Serratia marcescens, Stenotrophomonas maltophilia, Proteus mirabilis, Enterobacter* spp., and Methicillin-resistant *S. aureus*.

[b] Percentages may not add up to 100% as patients may have had >1 pathogen.

375) in the amoxicillin-clavulanate 2,000/125-mg treatment group and 7.8% (29 of 374) in the amoxicillin-clavulanate 875/125-mg treatment group had a classification of "severe." In the clinical PP test-of-cure population, 7.1% (14 of 198) of patients in the amoxicillin-clavulanate 2,000/125-mg treatment group and 4.8% (9 of 188) in the amoxicillin-clavulanate 875/125-mg treatment group had a GOLD classification of "severe" (27).

Overall rates of study completion were high in both groups. A total of 418 (94.4%) patients receiving amoxicillin-clavulanate at 2,000/125 mg, and 408 (90.7%) patients receiving amoxicillin-clavulanate at 875/125 mg completed the study. In the amoxicillin-clavulanate 2,000/125-mg treatment group, "lost to follow-up" was the most common reason for withdrawal from the study. In the amoxicillin-clavulanate 875/125-mg treatment group, the most common reason for withdrawal was "adverse event." Other reasons for withdrawal were insufficient therapeutic effect, protocol deviation, missed visit, serious adverse event, withdrawal of consent, baseline sign or symptom, and death. Compliance with study medication was also high in both groups. Overall, 97.1% of patients receiving amoxicillin-clavulanate at 2,000/125 mg and 94.7% of those receiving amoxicillin-clavulanate at 875/125 mg were compliant with treatment.

Bacteriology at screening. A total of 141 of 443 (31.8%) of patients in the amoxicillin-clavulanate 2,000/125-mg treatment group and 135 of 450 (30.0%) in the amoxicillin-clavulanate 875/125-mg treatment group had at least one pathogen identified at screening and were included in the bacteriology ITT population. The pathogens identified at screening are presented in Table 3.

The most commonly identified pathogen in both treatment groups was *H. parainfluenzae*, isolated in 29.1% (41 of 141) of patients with at least one pathogen receiving amoxicillin-clavulanate at 2,000/125 mg and 31.1% (42 of 135) of those receiving the comparator formulation. Other pathogens isolated in >15% of patients in each group were *H. influenzae* and *S. pneumoniae*. Individual patients may have had more than one isolate identified at screening.

Of the *H. parainfluenzae* isolates identified at screening, one (2.4%) in the amoxicillin-clavulanate 2,000/125-mg treatment group and five (11.1%) in the comparator group were β-lactamase positive. Six *H. influenzae* isolates in each treatment group (18.2 and 16.2%, respectively) were also β-lactamase positive. Of the *S. pneumoniae* isolates identified, four (14.3%) in the amoxicillin-clavulanate 2,000/125-mg treatment group were PRSP (penicillin MICs of ≥2 μg/ml), as were three (13.6%) in the amoxicillin-clavulanate 875/125-mg treatment group. The amoxicillin-clavulanate MICs for three (10.7%) *S. pneumoniae* isolates in the 2,000/125-mg treatment group and one (4.5%) in the comparator treatment group were ≥4/2 μg/ml, considered nonsusceptible (intermediate or resistant) to conventional amoxicillin-clavulanate formulations according to NCCLS criteria (24).

Clinical efficacy. The clinical success rates in the clinical PP population at test of cure (days 14 to 23, primary efficacy endpoint) was 93.0% (332 of 357) for amoxicillin-clavulanate at 2,000/125 mg and 91.2% (322 of 353) for amoxicillin-clavulanate at 875/125 mg (treatment difference, 1.8; 95% CI, −2.2, 5.7) (Fig. 1). As the lower limit of the 95% CI was no less than −10%, it can be concluded that the shorter, 5-day course of amoxicillin-clavulanate at 2,000/125 mg was at least as effective clinically as the 7-day course of amoxicillin-clavulanate at 875/125 mg in the treatment of AECB. The clinical results in the ITT population reflected those in the PP population. At test of cure, the clinical success rates were 88.5% (392 of 443) for amoxicillin-clavulanate at 2,000/125 mg and 86.4% (389 of 450) for amoxicillin-clavulanate at 875/125 mg (treatment difference, 2.0; 95% CI, −2.3, 6.4) (Fig. 1). Clinical success rates for other secondary endpoints are detailed in Table 4. In both the ITT and PP populations, the clinical success rates at the end-of-therapy and long-term follow-up visits supported the primary outcome that amoxicillin-clavulanate at 2,000/125 mg was at least as effective as amoxicillin-clavulanate at 875/125 mg in the treatment of AECB.

The clinical success among patients with a GOLD disease classification of "severe," was 100% (14 of 14) for amoxicillin-clavulanate at 2,000/125 mg compared with 77.8% (7 of 9) for amoxicillin-clavulanate at 875/125 mg in the clinical PP population at test of cure.

Per-patient bacteriological outcome. In the bacteriology PP population, amoxicillin-clavulanate at 2,000/125 mg achieved bacteriological success rates of >74% at all endpoints. Bacteriological results in the bacteriology ITT population were similar to those in the bacteriology PP population, with amoxicillin-clavulanate at 2,000/125 mg achieving bacteriological success rates of >70% at all endpoints. Bacteriological success rates for both amoxicillin-clavulanate formulations at all endpoints are shown in Table 4.

Per-pathogen bacteriological efficacy. The overall per-pathogen bacteriological success rates in the bacteriology PP population for amoxicillin-clavulanate at 2,000/125 and 875/125 mg are presented in Table 5. For the majority of pathogens, in both the amoxicillin-clavulanate 2,000/125- and 875/125-mg treatment groups, the determination of eradication at test of cure was based on clinical success (74.8 and 69.2%, respectively). Overall, 15.1 and 18.9% of pathogens isolated in the amoxicillin-clavulanate 2,000/125- and 875/125-mg treatment groups, respectively, were confirmed to be persistent or

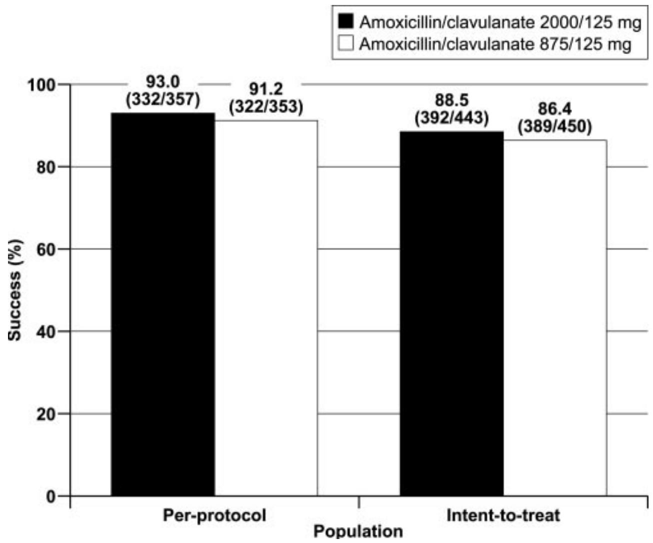

FIG. 1. Per-patient clinical success at the test-of-cure visit (days 14 to 21) for amoxicillin-clavulanate at 2,000/125 mg and 875/125 mg, respectively. The treatment differences were 1.8% (95% CI, −2.2, 5.7) for the PP population and 2.0% (95% CI −2.3, 6.4) for the ITT population.

recurrent at the test-of-cure visit, with a further 4.4 and 2.1%, respectively, presumed to be persistent or recurrent based on the patients' clinical signs and symptoms.

Against β-lactamase-positive isolates, bacteriological success rates in the PP population at test of cure were 91.7% for amoxicillin-clavulanate at 2,000/125 mg (1 of 1 for *H. parainfluenzae*, 5 of 5 for *H. influenzae*, 10 of 11 for methicillin-susceptible *S. aureus*, and 6 of 7 for *M. catarrhalis*) and 84.0% for amoxicillin-clavulanate at 875/125 mg (4 of 4 for *H. parainfluenzae*, 3 of 4 for *H. influenzae*, 8 of 9 for methicillin-susceptible *S. aureus*, and 6 of 8 for *M. catarrhalis*).

TABLE 5. Per-pathogen bacteriological success of amoxicillin-clavulanate at 2,000/125 and 875/125 mg against key pathogens at test of cure for the bacteriology PP population

Pathogen	% Bacteriological success (no. successful/total)	
	Amoxicillin-clavulanate at 2,000/125 mg	Amoxicillin-clavulanate at 875/125 mg
H. parainfluenzae	79.4 (27/34)	62.2 (23/37)
H. influenzae	86.2 (25/29)	75.0 (24/32)
S. pneumoniae	90.9 (20/22)	83.3 (15/18)
Methicillin-susceptible *S. aureus*	85.7 (12/14)	90.0 (9/10)
M. catarrhalis	75.0 (6/8)	81.8 (9/11)

Against *S. pneumoniae*, bacteriological success rates were 90.9% (20 of 22) and 83.3% (15 of 18) for amoxicillin-clavulanate at 2,000/125 and 875/125 mg, respectively, at test of cure. PRSP was isolated from three patients in the amoxicillin-clavulanate 2,000/125-mg treatment group and from two patients in the 875/125-mg treatment group at screening (PP test-of-cure population). Two of these patients in the amoxicillin-clavulanate 2,000/125-mg treatment group, including one who had PRSP for which the amoxicillin-clavulanic acid MIC was 4/2 μg/ml, and one in the 875/125-mg treatment group were bacteriological and clinical successes at test of cure.

PRSP treatment failures. The penicillin and amoxicillin-clavulanate MICs for the PRSP isolate from the one patient in the amoxicillin-clavulanate 2,000/125-mg treatment group who was a bacteriological and clinical failure at the test-of-cure visit were 8 μg/ml, and this isolate was also resistant to oral cephalosporins and macrolides. Although this PRSP isolate was eradicated, the patient was a bacteriological and clinical failure at test of cure due to the persistence of *H. influenzae*. The penicillin and amoxicillin-clavulanic acid MICs for the PRSP isolate from the patient in the amoxicillin-clavulanate 875/125-mg treatment group who was a bacteriological and clinical

TABLE 4. Success rates for amoxicillin-clavulanate at 2,000/125 and 875/125 mg at secondary endpoints

Treatment group[a]	% Success (no. successful/total)				
	Clinical[a]		Bacteriological[b]		
	End of therapy (days 9–11)	Long-term follow-up (days 28–35)	End of therapy (days 9–11)	Test of cure (days 14–21)	Long-term follow-up (days 28–35)
PP population with amoxicillin-clavulanate at:					
2,000/125 mg	95.8 (367/385)	89.7 (312/348)	80.5 (95/118)	76.7 (89/116)	74.8 (86/115)
875/125 mg	96.9 (354/369)	88.2 (298/338)	79.5 (93/117)	73.0 (81/111)	68.8 (75/109)
Treatment difference (95% CI)	−0.1 (−3.0, 2.7)	1.5 (−3.2, 6.2)	1.0 (−9.2, 11.2)	3.8 (−7.5, 15.0)	6.0 (−5.8, 17.7)
ITT population with amoxicillin-clavulanate at:					
2,000/125 mg	93.5 (414/443)	85/6 (379/443)	76.6 (108/141)	72.3 (102/141)	70.2 (99/141)
875/125 mg	92.7 (417/450)	81.8 (368/450)	77.0 (104/135)	69.6 (94/135)	65.9 (89/135)
Treatment difference (95% CI)	0.8 (−2.5, 4.1)	3.8 (−1.1, 8.6)	−0.4 (−10.4, 9.5)	2.7 (−8.0, 13.4)	4.3 (−6.7, 15.3)

[a] For clinical success, the PP population indicates the clinical PP population and for bacteriological success the bacteriology PP population. For bacteriological success, the ITT population indicates bacteriology intent-to-treat population.
[b] Includes all patients with ≥1 pathogen identified at screening.

failure were 2/1 μg/ml, and this isolate was resistant to oral cephalosporins and co-trimoxazole. This isolate persisted at the end-of-therapy visit and, as no further sputum samples were taken, was also recorded as a bacteriological failure at test of cure.

Safety. During the period on therapy and within 30 days posttherapy, AEs were reported by 36.6% (162 of 443) of patients receiving amoxicillin-clavulanate at 2,000/125 mg and 42.4% (191 of 450) of those receiving amoxicillin-clavulanate at 875/125 mg. The majority of AEs were mild to moderate in severity. Few patients were withdrawn from the study due to AEs (amoxicillin-clavulanate at 2,000/125 mg, 2.3%; amoxicillin-clavulanate at 875/125 mg, 4.0%). The most commonly reported AE in both groups was diarrhea. There was no statistically significant difference between the two treatment groups in the incidence of diarrhea (amoxicillin-clavulanate at 2,000/125 mg, 16.7%; amoxicillin-clavulanate at 875/125 mg, 14.4%; $P = 0.36$). All other AEs occurred in <5% of patients in either treatment group.

The incidence of SAEs was low in both the amoxicillin-clavulanate 2,000/125-mg and 875/125-mg treatment groups (2.0 and 3.3%, respectively). Only one patient, who was in the amoxicillin-clavulanate 875/125-mg treatment group, had an SAE of probable relationship to study medication (a suspected overdose).

There were no deaths in the amoxicillin-clavulanate 2,000/125-mg treatment group in the period on therapy and within 30 days posttherapy. Four deaths in this period occurred in the amoxicillin-clavulanate 875/125-mg treatment group, but none of these was considered to be of probable or suspected relationship to study medication. The recorded causes of death were gastrorrhagia, respiratory failure (two patients), and acute myocardial infarction.

DISCUSSION

In this randomized, double-blind, double-dummy, parallel group study, pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 mg given twice daily for 5 days was at least as effective clinically in the treatment of AECB as amoxicillin-clavulanate at 875/125 mg given twice daily for 7 days. Both treatments had high rates of clinical success in both the PP and ITT populations at all endpoints.

The GOLD guidelines recommend antimicrobial therapy for patients showing signs and symptoms of bacterial infection (27). This study was not, therefore, designed to evaluate the benefit of antimicrobial therapy versus no antimicrobial therapy in AECB but rather to compare the efficacy of the two amoxicillin-clavulanate formulations in cases where antimicrobial therapy would be considered appropriate and in line with currently accepted guidelines.

In this study, patients were required to be at least 45 years of age or greater than 40 years of age with more than 15 smoking pack years. These criteria were selected to ensure that patients recruited had a profile most consistent with underlying chronic bronchitis, thus increasing the chance of an infection that was bacterial in origin. However, only approximately 30% of patients in each treatment group had one or more pathogens isolated at screening, which is similar to results obtained in other studies (7, 28). This low recovery rate may be due, in this study, to the large number of sputum samples taken at screening that were unevaluable by Gram stain criteria (50%). It is worth noting that of the 221 sputum samples that did meet Gram stain criteria, 141 (63.8%) yielded a bacterial pathogen.

H. parainfluenzae was the most frequently isolated pathogen, followed by *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. Although the role of *H. parainfluenzae* in AECB is unclear, Sethi et al. have shown that in chronic bronchitis patients, infection with a new strain of *H. influenzae*, *S. pneumoniae*, or *M. catarrhalis* is associated with a more than twofold increase in the frequency of exacerbations (31). Effective therapy for AECB should therefore include coverage of these common pathogens when bacterial infection is thought to be the primary cause of the exacerbation.

Recent increases in antimicrobial resistance among respiratory pathogens in the community have become a global concern but may not be reflected in clinical trial populations. Despite the number of patients recruited, only seven PRSP isolates were found (14.0% of all *S. pneumoniae*), although this proportion is in line with other AECB studies (14, 31). A total of 6 (6.9%) *H. parainfluenzae*, 12 (17.1%) *H. influenzae*, 22 (75.9%) methicillin-susceptible *S. aureus*, and 25 (86.2%) *M. catarrhalis* isolates were β-lactamase positive.

Antimicrobial prescribing should aim to eradicate or maximally reduce the infecting pathogen, both to help treat the acute infection and perhaps to reduce the development and spread of resistant strains (4, 11, 15). Amoxicillin-clavulanate at 2,000/125 mg was bacteriologically effective against *S. pneumoniae* and *H. influenzae*, including resistant isolates. However, the number of resistant pathogens isolated in the study was too small to draw any conclusions.

As neither study drug would be expected to be effective in treating infections caused by atypical pathogens, patients were not screened for such pathogens. It is therefore not possible to determine if patients had coinfection with an atypical pathogen or if any such coinfection may have affected outcomes.

The majority of patients in this study were treated in the community, and few had a classification of severe disease: 13.8% of patients overall, similar to results reported by Adams et al. (2). In the present study, 100% of patients with a disease classification of severe who received amoxicillin-clavulanate at 2,000/125 mg were clinical successes, as were 77.8% of those treated with amoxicillin-clavulanate at 875/125 mg. The small number of patients in this category precluded statistical testing for significance, however. These rates of success reflect the findings from earlier studies (2, 3), but it is difficult to draw comparisons because of the low numbers of patients in this category and the variation in criteria used for disease classification between studies. Approximately 60% of patients in the present study had an FEV_1 of ≥50%. This would suggest that patients recruited in the present study were less severely ill than those in some previous studies (2, 3) and thus more likely to respond positively to treatment.

The appropriateness of using antimicrobial agents in treating AECB has been debated, as many episodes of AECB will be self-limiting (31). Additionally, not all patients may have bacterially caused AECB. This can mask the actual differences in efficacy between antimicrobials under investigation. In otitis media, this has been termed the "Pollyanna phenomenon" (21). Although this is of concern, it has been demonstrated that treatment of AECB with antimicrobials resulted in fewer treatment failures with deterioration than with placebo (3). Additionally, antimicrobial treatment of AECB has been shown to result in lower relapse rates, compared with no antimicrobial treatment (2). Such results suggest an important bacterial role in AECB. In addition, results from Adams et al. suggest that the choice of antimicrobial is a key factor affecting outcomes (2).

The present study compared a short, 5-day course of the new formulation of amoxicillin-clavulanate with a longer, 7-day course of a conventional formulation, although the double-blind design of the study meant that all patients took medication for the same duration. This study did not record compliance by day of therapy, so it is not possible to determine if compliance began to decline following day 5 in either treatment group. However, one suggested benefit of short-course therapy over standard therapy is the potential for improved patient compliance, and further investigations to assess the effects of short-course amoxicillin-clavulanate therapy on compliance and outcomes would be of value (18).

Both amoxicillin-clavulanate formulations were well tolerated in the current study, and the frequency and severity of AEs were similar for both treatment groups. Diarrhea was the only AE to occur in more than 5% of patients in either group. Few patients experienced SAEs or withdrew from the study due to AEs. These results support previous studies in which amoxicillin-clavulanate at 2,000/125 mg was shown to have a safety profile similar to that of conventional amoxicillin-clavulanate formulations (13, 30).

In conclusion, a short, 5-day course of pharmacokinetically enhanced amoxicillin-clavulanate at 2,000/125 mg was as effective clinically as the longer, 7-day course of amoxicillin-clavulanate at 875/125 mg in the treatment of adult patients with AECB and achieved high levels of bacteriological success, including against penicillin- and amoxicillin-resistant pathogens, with a comparable tolerability profile.

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